For calculation of the filing fee, claims 1-29 have been cancelled and replaced with new claims 30-49. Thus, no additional claims fee is necessary.

The specification has been amended as in the parent application.

Applicants respectfully request favorable reconsideration in view of the following remarks, which were presented in the parent application. Applicants have reiterated the following remarks to preserve the comments of record from the parent application.

In support of the remarks contained hereinbelow, a Declaration from the parent application has been submitted under 37 C.F.R. 1.132.

Applicants again request the Examiner to review the enclosed Declaration and reference which demonstrates the usefulness of antibody fragment $F(ab')_2$ in "targeting therapy".

Applicants believe that the specification clearly teaches one skilled in the art how to use the claimed antibody fragments, such as Fab'. Further, Applicants also strongly believe that it is well known to one skilled in the art how to use other antibody fragments, such as $F(ab')_2$ in view of the state of the art at the time of the priority date of the present application.

Based on the Examainer's comments, from the parent application, the Examiner believes that the use of the term "antibody fragment" encompasses subject matter which includes antibody fragments such as Fv, Fd, or $F(ab')_2$, which is not described in the specification. However, Applicants strongly believe that the specification clearly describes how to use Fab' fragments in the present invention, and how to use $F(ab')_2$ fragments for the purpose of the present invention.

It is well established in patent law that the specification does not need to literally describe "in ipsis verbis" the particular claim language in order for the specification to satisfy the written

description requirement of 35 USC § 112, first paragraph. See, for example, *In re Lukach* 169 USPQ 795, 796 (CCPA) 1971. Furthermore, it is sufficient that the specification "convey clearly to one skilled in the art, the information that the Applicant has invented the specific subject matter claimed". See, for example, *In re Wertheim* 191 USPQ 90, 96 (CCPA 1976) and *In re Ruschig* 154 USPQ 118, 123 (CCPA 1967).

It is appropriate for the claims to utilize claim language which does not readily appear in the specification as long as one skilled in the art would impliedly or inherently recognize that the Applicant has invented the specific subject matter claimed. In reviewing the teachings of the specification set forth on pages 1, 3, 12, 36, 37 and 41, it is clear that the inventors did contemplate a pharmaceutical composition or a liposome/antibody conjugate comprising an antibody fragment of the monoclonal antibody.

The specification teaches on page 11, line 18 to page 12, line 17 the method for binding an antibody to the surface of a liposome. It discloses as a preferred method a reaction of a thiolated antibody with a maleimide group existing in a liposome (see page 11, lines 21-24). As methods for thiolation, it teaches (1) the use of SPDP, iminothiolane (methyl-4-mercaptobutyrimidate), or mercaptoalkylimidate, which is conventionally used for thiolation of proteins (page 11, lines 21-24), and (2) reduction of the dithiol group intrinsic to an antibody (page 12, lines 6-9).

The second method (2) mentioned above comprises the use of the thiol group possessed by a Fab' antibody fragment which is formed by the reduction of a $F(ab')_2$ fragment as disclosed on page 12, lines 9-13 and page 36, line 16, page 37, line 5 (Section a. of Example 7) of the specification.

On the other hand, the first method (1) mentioned above, which is addressed to **thiolation of a protein having no thiol group, like $F(ab')_2$** is carried out in a conventional manner as described, for example, by Wright, S. et al., Advanced Drug Delivery Reviews, 3 (1989), pp. 343-352 (see especially on page 351, lines 18-22 and Table II), and by Traut, R.R. et al., Biochemistry, 12 (1973), p 3266-3273, copies of which have already been made of record in the parent application. Applicants have also demonstrated from the Declaration of T. Tagawa (Appendix III submitted January 26, 1998) that an Experiment conducted using an antibody-bonded PEG-modified liposome which was prepared by binding $F(ab')_2$ to a liposome in accordance with the above-mentioned Traut's method is clearly well within the state of the art at the time of the priority date and clearly show that the present inventors contemplated the present invention using other antibody fragments such as Fab' and $F(ab)_2$.

Applicants wish to remind the Examiner that the antibody fragments of the present invention must contain an antigen binding site for the purpose of the present invention. The current claims recite that the monoclonal antibody fragments must be bound to the surface of a liposome enclosing an anti-cancer agent or toxin and be capable of specifically binding to a surface antigen of a stomach and colon cancer cell membrane. Accordingly, the antibody or fragment thereof used in the claimed invention is defined by specific amino acid sequences.

Applicants also wish to advise the Examiner that the gist of the present invention resides in the finding of a specific monoclonal antibody defined by the amino acid sequences listed in the Sequence Listing, which can actually bind to the aimed antigen, and not in the finding that antibody fragments can also be used in the same manner as the antibodies themselves for the

purpose of the present invention. In other words, it is not necessary under U.S. practice for the present application to teach what is already widely known or recognized by those skilled in the art as of the priority date of the present application. Since it is well known to one skilled in the art that antibody fragments in the field of "targeting therapy" are used in the same manner as the antibody themselves, it clearly shows that the inventors contemplated the use of such fragments, as well as the antibodies themselves in the field of "targeting therapy". In support thereof, Applicants have submitted Dr. Hosokawa's Declaration in which the usefulness of antibody fragment $F(ab')_2$ in "targeting therapy" is experimentally shown. Further, a copy of the reference, Biochimica et Biophysica Acta (880 (1986) p72-77), which teaches the usefulness of $F(ab')_2$ in "targeting therapy" (see, in particular, Abstract of the article), as well as demonstrates that the use of $F(ab')_2$ in "targeting therapy" was already widely known and recognized by those skilled in the art as of the priority date of the present application. In other words, the enclosed Declaration and reference clearly demonstrate that the use of antibody fragments in "targeting therapy" as contemplated by the inventors was well known to one skilled in the art at the time of the invention.

Thus, since it is clear that the present inventors contemplated the use of all antibody fragments capable of specifically binding to the surface antigen of stomach and colon cancer cells for "targeting therapy", Applicants respectfully submit that the application is now in condition for allowance. Such action is thus, respectively solicited.

If, however, the Examiner has any suggestions for expediting allowance of the application or believes that direct contact with the Applicants' attorney will advance the prosecution of this case, the Examiner is invited to contact the undersigned at the telephone number below.

Respectfully submitted,

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December 21, 1999